UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,411	12/07/2000	Samy Ashkar	CMZ-124CP	1508

23579 7590 09/29/2005

PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,411	ASHKAR, SAMY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7, 16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/7/05 has been entered.

2. Claims 1, 3-5, 7, 16 and 18 are pending and under examination as they read on a method of inhibiting adhesion of a target cell to a substrate comprising providding the target cell with the adhesion modulatory peptided associated substrate SEQ ID NO:15 (inhibits VLA-4/VCAM interaction) such that adhesion of the target cell to the substrate is inhibited wherein the target cell is endothelial cells, neutrophil and macrophage and wherein the substrate is titanium, a polyvinyl surface, a gel, collagen, hyaluronic acid and PGA.

3. In order to facilitate the prosecution of this application, Applicant is requested to cancel all non-elected embodiments from the claims.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-5, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein !, von Willebrand's factor" claimed in claim 1, lines 2-3 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 1/07/05 points to the specification at pages 5-8 and 19-20 for support for the newly added limitations "glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein , von Willebrand's factor" as claimed in claim 1. However, the specification does not provide a clear support of such limitation with SEQ ID NO: 15. The Examiner notes that the specification on page 10, table II lists claimed VLEP of SEQ ID NO: 15 functions to inhibit VLA-4/VCAM interaction. Further, the specification on page 6, lines 6-17, discloses that alpha4/beta1 (VLA-4) is a receptor for fibronectin containing the CS-1 region which is situated within the IIICS region and VCAM-1. The Examiner was not able to find a clear support that claimed SEQ ID NO:15 inhibits binding of a cell to a

"glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein , von Willebrand's factor". The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

6. Claims 1, 3-5, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting binding of a neutrophil or macrophage cell to a fibronectin or to endothelial cells *in vitro*, with the adhesion peptide consisting of SEQ ID NO: 15, does not reasonably provide **enablement** for a method for inhibiting binding of any cell to any integrin or glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, Von Willebrand's factor, or vascular adhesion molecule comprising providing the cell with a peptide molecule comprising a a peptide having a molecule weight between 100 and 2500 Daltons and consisting of SEQ ID NO:15 in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification does not provide a sufficient enabling description of the claimed invention. The specification lacks empirical data to show an *in vivo* efficacy.

The specification discloses the amino acid sequences (SEQ ID NO:1-15 and SDV) with a various functional activity (e.g., pages 9-10, table II). The specification discloses that claimed SEQ ID NO:15 is involve in the inhibition of VLA-4/VCAM interaction.

Claim 1 recites that SEQ ID NO: 15 can be use to inhibit binding of any cell to any integrin, glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, von Willebrand's factor or any vascular adhesion molecule, however, the specification fails to provide guidance that the claimed SEQ ID NO: 15 can inhibit the interaction between any cell and those claimed counter receptors. The art does not recognize that the VLA-4 would bind to glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, von Willebrand's factor or any vascular adhesion molecule. The specification is not enabled for such inhibition with the claimed SEQ ID NO: 15. The specification fails to provide guidance on how SEQ ID NO: 15 would inhibit any cell to any counter receptor extracellular matrix protein.

The specification fails to enable a person of skill in the art to use any peptide of VLEP of SEQ ID NO: 15 to inhibit binding of any cell to any integrin or glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, Von Willebrand's factor, or vascular adhesion molecule, because claim 1 reads on the any cell, any integrin molecule and vascular adhesion molecule and specification offers no guidance as to what particular cells, integrins and vascular adhesion molecules, other than macrophage, endothelial cells, or neutrophil as the cell, $\alpha 4\beta 1$ (VLA-4) integrin, and VCAM-1 as the vascular adhesion molecule are involved in the method of inhibition with claimed SEQ ID NO:2.

Further, on the basis of the disclosed correlation of the level of claimed VLEP peptide of SEQ ID NO: 15 and the inhibition of VLA-4/VCAM interaction observation alone, applicant concludes that the scope of the VLEP peptide of SEQ ID NO: 15 encompassed by the claimed invention can have biological activity to inhibit binding of any cell to any integrin or glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, Von Willebrand's factor, or vascular adhesion molecule. In addition Applicant concluded that the claimed peptide of SEQ ID NO: 15 can be provided as pharmaceutical compositions to subjects including human to effectively inhibit binding of any cell

The specification discloses the inhibition of interaction of the two cell adhesion counter receptors VLA-4 and VCAM-1 to be useful to induce apoptosis in adhesion-dependent cells (see pg 18, lines 16-17). The exemplification is drawn to inhibit firm adhesion of endothelial cell to heparn sulfate or ICAM molecules with SEQ ID NO: 1 (see page 19, lines 5-11), use of SEQ ID NO: 3 to treat fibrosis (see pg 19, lines 15-16), and use of SEQ ID NO: 5 in vascularization (see page 19, lines 18-20). No assay that recapitulates physiologic conditions is provided.

In addition, for one to successfully use claimed VLEP peptide of SEQ ID NO:1 in vivo, which is suggested to work by blocking cell surface receptors, it is essential to understand what conditions are of interest to treat, if those molecules targeted participant in those conditions in vivo, what blocking intervention is most appropriate and the general criteria which will define quantitative endpoints for accessing efficacy (see Ward et al., page 166, section on "Strategies..", in particular). While the specification relies upon assertion that the claimed VLEP peptide of SEQ ID NO: 15 inhibits VLA-4/VCAM interaction (see table II of the instant specification); there is insufficient guidance and direction in the specification for diseases or conditions that would be targeted with claimed VLEP peptide of SEQ ID NO: 15 outside of the general category of "inflammation" (see page 6, lines 7-17 in particular). The specification does not teach how to extrapolate such assertion (see table II) to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention.

Although Applicant's specification describes certain peptide examples involved in binding of cell via an integrin, there is no correlation on this record between such examples and a practical use in currently available form for humans or animals. It is not enough to rely on such examples where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to use in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746. There must be a rigorous correlation of biological activity between the asserted use and in vivo use to establish practical use.

The lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective peptide-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting binding of a cell to a target molecule using peptides.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 1/07/05, have been fully considered, but have not been found convincing.

Applicant submits that there may not be proof that the method works in all situations is not sufficient to make the claim non-enabled. It is very clear the claim is enabling in vitro and in cell culture and the studies provided here are of the type to be reasonably predictive of success in an animal based on comparisons to other similar situations. Applicant submits that there are many peptides that are routinely administered to individual for use in blocking binding, including RGD peptides and inhibitors of selectins. Further applicant contends that the facts in this application are quite similar to those situations. Applicant points that the examiner has provided no basis for the rejection other than that there is no animal or human data. Applicant submits that this does not meet the legal standard.

However, the specification only asserts the function of the claimed SEQ ID NO: 15 in the inhibition of VLA-4/VCAM interaction (see table II in particular). However, the specification fails to provide empirical data showing such inhibition in vitro, let alone in vivo data including animal. RGD and selectin peptides are not claimed and therefore irrelevant to the claimed invention. Further the art is full of examples wherein the RGD peptide for example, does not work in vivo. Klotz *et al* teaches a method to asses therapeutic potential of alpha(v)-integrin antagonists LM609 and cRGDfV in neovascularization of the anterior segment, their inhibitory effect on angiogenesis was studied in two rat models for corneal neovascularization (within a cell). Klotz et al further teach that in corneas with silver nitrate burns, systemic cRGDfV treatment showed no significant reduction of vascularization compared with controls and that pellets containing bFGF and LM609 mAb induced significatntly less neovasculaization than pellets containing bFGF and control mAb. Further, the specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy. Therefore, enablement of the claimed VLEP peptide of SEQ ID NO: 15 cannot be based on similar situations as those for example RGD peptides. The peptide itself has to be enabled for in vivo use.

Applicant submits that claim 1 now has been limited to a method of inhibiting cell binding outside of a subject (emphasis added by Applicant). Applicant submits that the specification is indeed enabling for the in vitro use of the peptide molecules.

While the specification enables the use claimed SEQ ID NO: 15 to inhibit binding of a neutrophil or macrophage cell to a fibronectin or to endothelial cells *in vitro*. However, claim 1 still reads on *in vivo* method in the absence of clear indication that the claimed method is limited to *in vitro* inhibition of binding.

Applicant points out to SEQ ID NOs: 6, 8, 10, 12 and 14. However, these sequences are drawn to non-elected invention and are not under examination in the instant application.

7. Claims 1, 3-5, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of inhibiting binding of a neutrophil or macrophage cell to a fibronectin or to endothelial cells *in vitro*, with the adhesion peptide consisting of SEQ ID NO: 15.

Applicant is not in possession of a method for inhibiting binding of any cell to any integrin or glycosaminoglycan, fibrinogen, collagen, vitronectin, thrombospondin, osteopontin, bone sialoprotein I, Von Willebrand's factor, or vascular adhesion molecule comprising providing the cell with a peptide molecule comprising a a peptide having a molecule weight between 100 and 2500 Daltons and consisting of SEQ ID NO:15 in claim.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (integrin, glycosaminoglycan, or vascular adhesion molecule) to describe the claimed genus, nor does it provide a description of structural features that are common to species (integrin, glycosaminoglycan, or vascular adhesion molecule). As discussed above, the specification provides no structural description of integrin, glycosaminoglycan, or vascular adhesion molecule other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed integrin, glycosaminoglycan, or vascular adhesion molecule looks like. The specification's disclosure is inadequate to describe the claimed genus of integrin, glycosaminoglycan, or vascular adhesion molecule.

Applicant has disclosed only SEQ ID NO: 15 inhibits VLA-4 and VCAM-1interaction; therefore, the skilled artisan cannot envision all the contemplated integrin, vascular adhesion molecule or glycosaminoglycan possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 23, 2005

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600